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Incidence and Significance of Ventricular Tachycardia and Fibrillation in the Absence of Hypotension or Heart Failure in Acute Myocardial Infarction Treated With Recombinant Tissue-Type Plasminogen Activator: Results From the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial

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Objectives. **The purpose of this study was to determine the incidence of ventricular tachycardia and fibrillation without hypotension or heart failure after treatment with recombinant tissue-type plasminogen activator (rt-PA), anatomic correlates of their development, the effect of immediate intravenous metoprolol on their occurrence and the outcome of patients with these arrhythmias.**

Background. **Malignant arrhythmias after thrombolytic therapy have been reported to occur as a result of coronary reperfusion, which is associated with reduced mortality in patients receiving thrombolytic therapy.**

Methods. **We analyzed data from 2,546 patients in the Thrombolysis in Myocardial Infarction (TIMI) Phase II trial without congestive heart failure or hypotension during the 1st 24 h after study entry. Forty-nine patients (1.9%) developed sustained ventricular tachycardia or ventricular fibrillation within 24 h of study entry (group 1), and 2,497 patients (98.1%) did not (group 2).**

Results. **Baseline characteristics and admission laboratory values were similar in the two groups. In patients undergoing protocol angiography 18 to 48 h after rt-PA, the infarct-related artery was patent in a greater percent of group 2 patients (87% [1,015 of 1,169]) than group 1 patients (68% [15 of 22], $p = 0.01$), although angiography was performed less frequently in group 1 than in group 2. More group 1 than group 2 patients died within 21 days (20.4%) (1.6%, $p < 0.001$). For patients surviving to 21 days, there was no difference in mortality between patients in the two groups in the following year.**

Conclusions. **Ventricular tachycardia and fibrillation are not markers for reperfusion after thrombolytic therapy. These arrhythmias are associated with occlusion, not patency, of the infarct-related artery. Early mortality is increased in patients who develop ventricular tachycardia and fibrillation, even in the absence of congestive heart failure and hypotension.**

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During the early phase of acute myocardial infarction, malignant ventricular arrhythmias occur in the absence of heart failure or hypotension in 2% to 8% of patients (1–5). These arrhythmias were a common cause of death in patients admitted to the hospital during acute myocardial infarction before the development of coronary care units and defibrillators in the 1960s. Currently, ventricular arrhythmias in the absence of heart failure or hypotension are an infrequent cause of death during the hospital period for acute myocardial infarction. These malignant ventricular arrhythmias have traditionally been believed to be easily terminated with cardiac defibrillation and without important prognostic significance (6–12).

Malignant arrhythmias have been reported to occur after streptokinase therapy as a result of coronary reperfusion (13–16). Little is known about the incidence and significance of ventricular tachycardia and fibrillation after intravenous recombinant tissue-type plasminogen activator therapy (rt-PA). These may be different from what has been reported after streptokinase therapy. Compared with intravenous streptokinase, intravenous rt-PA results in more rapid reperfusion, which might influence the development of malignant ventricular arrhythmias (17).

We undertook the present study, a data bank analysis of patients enrolled in phase II of the Thrombolysis in Myocardial Infarction (TIMI I) trial to determine the incidence of ventricular tachycardia and fibrillation in the absence of

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congestive heart failure and hypotension after treatment with rt-PA, the anatomic correlates of their development, the effect of immediate intravenous metoprolol on their occurrence and the outcome of patients with these arrhythmias.

Methods

Inclusion criteria. Inclusion criteria for the TIMI II trial have been reported elsewhere (18). Briefly, these criteria included age <76 years, 30 min of chest discomfort suggestive of acute myocardial ischemia, ST segment elevation >1 mV in two contiguous leads, presentation within 4 h of the onset of chest pain; and informed written consent by the patient. Exclusion criteria for TIMI II included a history of cerebrovascular disease, blood pressure >180 mm Hg systolic or 110 mm Hg diastolic, a bleeding disorder, surgery within the previous 2 weeks, recent prolonged cardiopulmonary resuscitation, percutaneous transluminal coronary angioplasty or severe trauma within the preceding 6 months, previous cardiac surgery, left bundle branch block, dilated cardiomyopathy or other serious illness.

Patients received rt-PA therapy (150 mg for 6 h in the first 520 patients; 100 mg for 6 h in the remaining 2,819 patients) and were also randomly assigned to undergo either catheterization and coronary angioplasty (or coronary bypass graft surgery, if indicated) 18 to 48 h after treatment with rt-PA (invasive strategy) or no routine coronary angiography (conservative strategy). Patients assigned to the conservative strategy underwent catheterization and revascularization if ischemia recurred despite medical therapy during the hospital period or if ischemia was provoked during a predischarge exercise test. Patients received lidocaine, 75-mg intravenous bolus, followed by a 2- to 4-mg intravenous infusion for at least the 1st 24 h of the hospital period.

Eligible patients at participating centers were randomly assigned to either immediate intravenous beta-adrenergic blocking agent therapy (three 5-mg intravenous injections at 2-min intervals, followed by oral metoprolol, 50 mg twice a day for the 1st day, followed by 100 mg twice a day thereafter) or deferred beta-blocker therapy (50 mg of oral metoprolol twice a day on day 6 and 100 mg twice a day thereafter) (19). Patients were excluded from randomization in the beta-blocker substudy of the trial (TIMI IIB) if they were being treated with a beta-blocker, verapamil or diltiazem at the time of entry into the TIMI trial or had contraindications to intravenous beta-blockers, including ventricular rate <55 beats/min, systolic blood pressure <90 mm Hg, moist rales covering greater than one-third of the lung fields, asthma, first-degree heart block >0.24 ms or higher degrees of atrioventricular block.

In this study, only ventricular tachycardia and ventricular fibrillation occurring within 24 h of study entry in the absence of hypotension or heart failure, requiring cardioversion or defibrillation, were included for analysis.

Left ventricular ejection fraction was determined by equilibrium radionuclide ventriculography performed a mean of 9.2 days after admission to the hospital (20). The cause of death in each patient was determined by the Mortality and Morbidity Classification Committee of the TIMI trial.

Patient selection. Patients randomized to the conservative and invasive strategies, regardless of their eligibility for randomization to beta-blocker therapy, were considered for this analysis. From the pool of patients enrolled in TIMI II, patients were included in our study if they were without congestive heart failure or hypotension during the 24 h after admission to the hospital. Patients who had ventricular tachycardia or fibrillation before enrollment in the trial and the administration of rt-PA were excluded from analysis.

Statistics. The results presented in this report are based on the TIMI data analysis files as of January 1991. All analyses were performed using the SAS package (21). To account for the effects of multiple testing, p values between 0.01 and 0.001 were judged to provide some evidence of group differences, and p values < 0.001 were judged to provide strong evidence of group differences not due to chance alone. Patients with and without ventricular tachycardia and fibrillation were compared using the Student *t* test or Wilcoxon tests for continuous variables and chi-square tests (or the Fisher exact test when numbers were small) for proportions. Event rates were computed using the Kaplan-Meier method (22) and compared using the log-rank test statistic. Comparison of ejection fraction between patients with and without ventricular tachycardia and fibrillation is potentially biased because of missing data. To account for all patients who entered the study, a composite outcome measure was defined by death within 21 days, survival to 21 days without a hospital discharge radionuclide ventriculogram or a hospital discharge radionuclide ventriculogram with left ventricular ejection fraction ≤55% and a chi-square test with 1 degree of freedom performed to compare the percents of patients with a left ventricular ejection fraction >55% (i.e., who did not have any component of the composite, unfavorable outcome). For descriptive purposes, further details of the observed ejection fractions are displayed in Table 5, but probability inferences are not appropriate comparing the percent of patients within each category making up the composite outcome.

Results

Study patients. Of the 3,339 patients in TIMI II, 331 had congestive heart failure or hypotension before treatment with rt-PA, and 175 developed ventricular tachycardia or fibrillation before the administration of rt-PA (150 without congestive heart failure or hypotension and 25 with congestive heart failure or hypotension), these patients were excluded from analysis. Of the remaining 2,858 patients, 312 patients (10.9%) developed congestive heart failure or hypotension during the 1st 24 h of the hospital period, and these patients were also excluded. The remaining 2,546 patients form the basis of this report. Of these patients, 49 (1.9%)

Table 1. Baseline Characteristics of the Total Study Group (2,546 patients without congestive heart failure or hypotension during the 24 h after admission)

	VT/VF (n = 49)	No VT/VF (n = 2,497)	p Value
Mean age (yr)	55.1 ± 11.4	56.3 ± 10.2	NS
Male	43 (88)	2,089 (84)	NS
Not low risk	26 (53)	1,517 (61)	NS
Age ≥70 yr	6 (12)	263 (11)	NS
Previous myocardial infarction	6 (12)	264 (11)	NS
Anterior infarction	17 (35)	1,210 (48)	NS
Atrial fibrillation or flutter	2 (4)	40 (2)	NS
Previous angina	25 (51)	1,355 (54)	NS
Previous congestive heart failure	0 (0)	43 (2)	NS
History of diabetes mellitus	3 (6)	309 (12)	NS
History of hypertension	19 (39)	961 (38)	NS
Current smoking	32 (65)	1,212 (49)	0.02
Admission heart rate (beats/min)	74.3 ± 16.2	74.8 ± 15.5	NS
Time from pain onset to rt-PA therapy (h)	2.48 ± 1.07	2.64 ± 0.85	NS
Treated within 2 h of pain onset	20 (41)	642 (26)	0.02

Continuous variables are expressed as mean value ± SD or number (%). NS = p > 0.10; rt-PA = recombinant tissue-type plasminogen activator; VT/VF = ventricular tachycardia/ventricular fibrillation.

developed either ventricular tachycardia (35 patients) or ventricular fibrillation (14 patients) within 24 h of study entry (group 1), and 2,497 patients (98.1%) did not (group 2).

Baseline characteristics (Table 1). There were no significant differences between groups 1 and 2 in any of the variables analyzed, except for current smoking, which tended to be more frequent in group 1 (65%) than in group 2 (49%) (p = 0.02). Anterior infarction was present in 17 (35%) of 49 group 1 patients and in 1,210 (48%) of 2,497 group 2 patients (p = NS). Ventricular tachycardia and fibrillation occurred in 17 (1.4%) of 1,227 patients with anterior infarction and in 32 (2.4%) of 1,319 patients with inferior infarction (p = NS). Diabetes mellitus was present in 3 (6%) of 49 patients in group 1 and in 309 (12%) of 2,497 patients in group 2 (p = NS). The mean time to treatment was similar in both groups. However, when time to treatment was analyzed as a discrete variable, 41% of group 1 patients versus 26% of group 2 patients received treatment within 2 h of the onset of chest pain (p = 0.02).

Medical therapy (Table 2). There were no significant differences between groups 1 and 2 with regard to medical therapy that patients received in the week before admission to hospital.

Laboratory values (Table 3). The mean serum potassium level in group 1 was 3.82 ± 0.07 versus 3.97 ± 0.01 mEq/liter in group 2 (p = 0.03) (Table 3). Group 1 patients tended to have a slightly higher peripheral white blood cell count (12.0×10^9/liter) compared with group 2 (10.9×10^9/liter, p = 0.01), but there was no evident difference in white blood cell count between groups 1 and 2 (p = 0.21) after accounting for differences between the groups for current smoking status with an analysis of variance. When analyzed as a discrete variable, there was no difference in the frequency of a white blood cell count $>15.0 \times 10^9$/liter between the two groups. The mean platelet count and serum creatinine were also similar in the two groups.

Hospital course (Tables 4 and 5). The 21-day mortality rate in group 1 was increased (20.4% [10 of 49]) compared with group 2 (1.6% [40 of 2,497], p < 0.001) (Table 4). Six of 10 deaths in group 1 occurred within 24 h. Two deaths occurred in patients with ventricular rupture that was found at autopsy, and four deaths resulted from either unsuccessful resuscitation after cardiac arrest or recurrent cardiac arrest shortly after successful resuscitation. In none of the four patients with ventricular tachycardia and fibrillation who survived >24 h and died within the 1st 21 days was death due to arrhythmia. There was no significant difference in the reinfarction rate between the two groups.

There were no significant differences in the proportion of patients with left ventricular ejection fraction >55% on

Table 2. Medical Therapy in the Week Before Admission in the Total Study Group

	VT/VF (n = 49)		No VT/VF (n = 2,497)		p Value
	No.	%	No.	%	
Beta-adrenergic blocking agents*	8	16	459/2,492	18	NS
Calcium blocking agents*	7	14	345/2,493	14	NS
Aspirin	5	10	369	15	NS
Diuretic agents*	7	14	377/2,494	15	NS
Cardiac glycosides	2	4	48	2	NS
Oral vasodilators/nitrate therapy	5	10	270	11	NS

*Different denominators reflect missing data in some patients. Abbreviations as in Table 1.

Table 3. Laboratory Values Obtained on Hospital Admission Before the Administration of Recombinant Tissue-Type Plasminogen Activator in the Total Study Group

	VT/VF (n = 49)	No VT/VF (n = 2,497)	p Value
Potassium (mEq/liter)	3.82 ± 0.46	3.97 ± 0.49	0.05
≥5.0*	[illegible]	65/2,395 (3)	NS
<3.5*	9/43 (21)	310/2,395 (13)	NS
Mean white blood cell count (× 10⁹/liter)	12.0 ± 3.0	10.9 ± 3.8	0.01
White blood cell count ≥15.0 (× 10⁹/liter)*	6/46 (13)	319/2,415 (13)	NS
Platelet count (× 10⁹/liter)	294 ± 65	284 ± 98	NS
Creatinine (mg/dl)	1.13 ± 0.28	1.12 ± 0.27	NS

*Different denominators reflect missing data in some patients. Continuous variables are expressed as mean value ± SD or number (%) of patients. Abbreviations as in Table 1.

predischarge radionuclide ventriculography between the two groups (Table 5). However, more patients in group 1 died before undergoing radionuclide ventriculography.

Immediate intravenous beta-blocker therapy. Of the 2,546 patients in the total study group, 1,208 were eligible for random assignment to either immediate intravenous beta-blocker therapy or deferred oral beta-blocker therapy beginning on the 6th hospital day. Among patients assigned to receive immediate intravenous beta-blocker therapy, the frequency of ventricular tachycardia or fibrillation was 2.0% (12 of 602), similar to the 1.3% incidence (8 of 606) in those assigned to receive oral beta-blocker therapy beginning on the hospital day 6 (p = NS).

Anatomic data (Table 6). Angiographic data from protocol cardiac catheterization at 18 to 48 h were obtained for 1,191 (92%) of 1,295 patients randomly assigned to the invasive strategy, including 22 (79%) of 28 patients with ventricular tachycardia and fibrillation and 1,169 (92%) of 1,267 patients without ventricular tachycardia or fibrillation (Table 6). Of the patients who did not complete randomly assigned protocol cardiac catheterization, 3 of 6 patients with and 4 of 96 patients without ventricular tachycardia and fibrillation died within the 1st 72 h. Of the patients with angiographic data, the infarct-related artery was patent (TIMI flow grade 2 or 3) in fewer patients in group 1 (15 [68%] of 22) than in group 2 (1,015 [87%] of 1,169, p = 0.01).

Table 4. Event Rates at 21 Days in the Total Study Group According to the Presence or Absence of Ventricular Tachycardia or Fibrillation

	VT/VF (n = 49)		No VT/VF (n = 2,497)		p Value
	No.	%	No.	%	
Reinfarction	5	10.2	155	6.2	NS
Death	10	20.4	40	1.6	< 0.001
Death or reinfarction	13	26.5	184	7.4	< 0.001

Abbreviations as in Table 1.

Table 5. Composite Outcome at 21 Days (mortality, absence of a radionuclide study and left ventricular ejection fraction <55%) in the Total Study Group According to the Presence or Absence of Ventricular Tachycardia or Fibrillation

	VT/VF (n = 49) No. (%)	No VT/VF (n = 2,497) No. (%)	p Value
Dead ≤21 days, alive with no study by 21 days or no LVEF from study	19 (38.8)	369 (14.8)	
LVEF			
<35%	0 (0.0)	194 (7.8)	
35% ≤ EF ≤ 55%	19 (38.8)	1,073 (43.0)	
>55%	11 (22.4)	861 (34.5)	0.08*

*p value from 1-degree of freedom test for difference in percent with left ventricular ejection fraction >55% (i.e., without death <21 days after entry, no left ventricular ejection fraction measured or left ventricular ejection fraction <55%). LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

Multivessel disease was present in approximately one third of patients in both groups, and there was no significant difference between the groups with regard to location of the infarct-related artery.

Medications at discharge (Table 7). At the time of hospital discharge, there was a tendency for diuretic agents to be prescribed more frequently and aspirin less frequently in group 1 patients (p = NS). Antiarrhythmic medications tended to be prescribed more frequently in group 1 patients as well.

Follow-up. Among patients who survived the 1st 3 weeks after infarction, the mortality rate during the period from 21 days to 1 year was similar in groups 1 and 2 (5.1% [2 of 39] vs. 2.1% [52 of 2,457], respectively, p = NS).

Discussion

Principal findings. The most important findings of this study are that 1) sustained ventricular tachycardia or ven-

Table 6. Anatomic Characteristics in 1,193 Patients in the Total Study Group Randomly Assigned to the Invasive Strategy Who Received Protocol Catheterization 18 to 48 h After Administration of Recombinant Tissue-Type Plasminogen Activator

	VT/VF (n = 22)		No VT/VF (n = 1,171)		p Value
	No.	%	No.	%	
Patent infarct artery*	15/22	68	1,015/1,169	87	0.01
Multivessel disease*	7	32	362/1,136	32	NS
Infarct-related artery					NS
LAD	5	23	466	40	
RCA	14	64	543	46	
LCx	3	14	153	13	
LMCA	0	0	2	0.2	
Unknown	0	0	7	0.6	

*Different denominators reflect missing data in some patients. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery.

Table 7. Medications Prescribed for the Total Study Group at the Time of Hospital Discharge

	VT/VF (n = 39)		No VT/VF (n = 2,457)		p
	No.	%	No.	%	Value
Beta-adrenergic blocking agents	30	77	1,736	71	NS
Calcium blocking agents	15	39	1,110	45	NS
Cardiac glycosides	5	13	203	8	NS
Diuretic agents	6	15	158	6	0.03
Aspirin	32	82	2,230	91	0.07
Antiarrhythmic agents	5	13	153	6	0.10

Abbreviations as in Table 1.

tricular fibrillation resulting in cardiac arrest occurred infrequently in patients treated with rt-PA and appeared to be associated with occlusion rather than patency of the infarct-related artery on angiography 18 to 48 h after rt-PA administration, and 2) the 21-day mortality rate in patients with these malignant arrhythmias was increased, compared with that in patients without these arrhythmias, primarily because of inability to resuscitate these patients from the index arrhythmia.

Previous placebo-controlled studies. Two large controlled trials of thrombolytic therapy have also revealed a low frequency of ventricular fibrillation in the absence of hypotension or heart failure in patients receiving thrombolytic therapy, similar to the frequency occurring in patients not receiving thrombolytic therapy (5,23). In the Gruppo Italiano per lo Studio della streptochinasi nell'Infarto Miocardico (GISSI) trial, patients were included in the analysis if they developed ventricular fibrillation and were without hypotension or heart failure at the time of admission to hospital for a first myocardial infarction (5). No attempt was made to identify and exclude patients who developed congestive heart failure or hypotension after admission, before ventricular fibrillation. Of the 7,113 patients included in that analysis, 3,599 patients received intravenous streptokinase, and 3,514 control patients received no thrombolytic therapy. The frequency of ventricular fibrillation in the 48 h after admission was 4.5% in the group receiving intravenous streptokinase, similar to the 4.8% frequency in the control group. The mortality rate in patients with ventricular fibrillation was 10.8%, nearly twice that in patients without ventricular fibrillation (5.9%). Investigators from the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) trial reported an analysis of continuous Holter ECG monitoring performed in a subset of 309 patients from one participating center in the trial (23). Although frequent ventricular premature beats occurred more often in patients receiving the thrombolytic agent rt-PA, ventricular fibrillation during the 1st 24 h occurred in 4 (2.5%) of 158 patients who received thrombolytic therapy, similar to the 5 (3.3%) of 151 patients assigned to receive placebo. Neither the GISSI nor ASSET trials included routine coronary angiography after thrombolytic therapy, and therefore a relation between patency rates and ventricular fibrillation could not be established.

In TIMI II, all patients received intravenous rt-PA within 4 h of the onset of symptoms. Therefore, no control group was available to determine the frequency of ventricular tachycardia or fibrillation in patients who did not receive thrombolytic therapy. However, 50% of patients in the trial were randomly assigned to coronary angiography 18 to 48 h after administration of rt-PA. The difference in the percent of patients with patent infarct-related arteries on protocol cardiac catheterization in the groups with and without ventricular tachycardia and fibrillation suggests that reperfusion does not increase, and may in fact decrease, the occurrence of ventricular tachycardia and fibrillation. These anatomic data should be viewed with caution because of the disproportionate amount of missing data in those patients with ventricular tachycardia and fibrillation. If all of the patients with ventricular tachycardia and fibrillation who did not undergo randomly assigned protocol cardiac catheterization had patent arteries, and all of the patients without ventricular tachycardia and fibrillation who did not undergo randomly assigned protocol cardiac catheterization had occluded arteries, the difference between the percent of patients with patent infarct-related arteries in patients with and without ventricular tachycardia and fibrillation could be as small as 1%. The TIMI II data do not support the hypothesis that reperfusion increases the occurrence of ventricular tachycardia and fibrillation, even if they do not conclusively establish an association between ventricular tachycardia and coronary occlusion.

Reperfusion arrhythmias in animal models. Numerous animal models of myocardial infarction (24,25) have documented that reperfusion arrhythmias do occur. These models have generally required that acute ischemia be present in >25% of the myocardium and that reperfusion be completed within 10 to 25 min of the onset of ischemia for arrhythmias to reliably be provoked by reperfusion (26–29). The degree to which these animal models resemble the clinical setting is limited, and the many differences may account for the disparity between the results from these animal models and those of several large clinical trials that reveal that reperfusion therapy does not increase (5,23), and may in fact decrease (30), the incidence of ventricular tachycardia and fibrillation.

Influence of lidocaine. Patients in TIMI II received intravenous lidocaine immediately before administration of rt-PA (18). Lidocaine was not routinely administered in either the GISSI or ASSET trials (5,23). Whether lidocaine therapy reduces ventricular tachycardia or fibrillation in the early phases of acute myocardial infarction (31), and specifically after thrombolytic therapy, remains controversial. Lidocaine has been shown to be ineffective in reducing reperfusion-induced ventricular fibrillation in several different animal models of infarction (32).

Clinical correlates of ventricular tachycardia and ventricular fibrillation. In the GISSI trial, ventricular tachycardia and fibrillation in the absence of heart failure and hypotension occurred 50% more frequently in patients with inferior than in those with anterior myocardial infarction (3.7% vs. 2.5%, respectively) (5). A similar trend existed in TIMI II, in which ventricular tachycardia and fibrillation in the absence of heart failure and hypotension occurred in 32 (2.4%) of 1,332 patients with inferior infarction and 17 (1.4%) of 1,229 patients with anterior infarction. However, in TIMI II, these differences could have been due to chance; TIMI II was smaller and may have lacked the power to detect this association.

In the Multicenter Investigation of the Limitation of Infarct Size trial, ventricular tachycardia and fibrillation in the absence of heart failure and hypotension occurred less frequently in patients with diabetes mellitus (2 [1.4%] of 147) than in patients without diabetes mellitus (38 [5.7%] of 668, $p < 0.05$) (2). In TIMI II, although ventricular tachycardia and fibrillation in the absence of heart failure and hypotension also occurred in a smaller proportion of patients with (3 [1.0%] of 312) than without diabetes (46 [2.1%] of 2,234), the difference could have been due to chance. A slightly lower mean serum potassium level was found in the group of patients who developed ventricular tachycardia and fibrillation in our study. This difference in potassium levels was neither clinically nor statistically significant. Hypokalemia (potassium <3.5 mEq/liter), a well recognized risk factor for malignant ventricular arrhythmias, was present on study entry in a similar proportion of patients in both groups. In our study, the peripheral white blood cell count tended to be higher in patients who developed ventricular tachycardia and fibrillation than in patients without these arrhythmias ($12.0 \pm 0.4 \times 10^9$/liter vs. $10.9 \pm 0.1 \times 10^9$/liter, $p < 0.01$), but this difference was not significant ($p = 0.21$) after adjustment for current smoking status. Smokers have been shown to have higher white blood cell counts than those of nonsmokers (33).

The TIMI IIB study of immediate intravenous beta-blocker therapy versus deferred oral beta-blocker therapy did not show a difference between the randomly assigned treatment groups in the occurrence of ventricular tachycardia or fibrillation in the absence of heart failure and hypotension. However, the TIMI IIB study had limited power to detect differences in infrequent outcomes, such as ventricular tachycardia and fibrillation, and therefore provides little information concerning the efficacy of immediate intravenous beta-blocker therapy in preventing these arrhythmias. Further studies are needed to determine the exact mechanism of ventricular tachycardia and fibrillation occurring after reperfusion therapy in humans and the effect of beta-blockers on these arrhythmias.

Increased mortality associated with ventricular tachycardia and ventricular fibrillation. The increased mortality in patients in TIMI II with ventricular tachycardia and fibrillation is in disagreement with some (6,12,34), but not all (4,5,35,36) previous studies. Patients in TIMI II were admitted to coronary care units during the 1st 24 h of admission; therefore, arrhythmias should have been promptly detected even though resuscitative efforts were not always successful. In the GISSI trial, it could not be determined whether ventricular fibrillation, which was associated with a twofold increase in mortality, was a marker for patients at increased risk for death or the direct cause of the increased mortality (5). The TIMI II data suggest that in most patients, death resulted from inability to resuscitate patients from their arrhythmias. In two patients, myocardial rupture had occurred. However, in the remaining patients, it is not clear why these arrhythmias in patients with acute myocardial infarction without any evidence of pump failure could not quickly be terminated by defibrillation. Animal studies (25) have shown that ventricular fibrillation after reperfusion is more likely to occur in the presence of severe ischemia in the ischemic zone. Studies in humans have shown that ventricular tachycardia and fibrillation are more likely to occur in patients with a larger infarct size, as determined by serum cardiac enzyme levels (4,37,38). These data may explain in part why, in some patients, these arrhythmias could not be terminated. However, the mortality rate in patients who survived the initial 21 days after myocardial infarction was low in the following year and was not significantly different in patients with and without ventricular tachycardia and fibrillation, a finding in agreement with most previous studies (8,11,39).

Study limitations. In the TIMI II trial, there was no systematic data collection with regard to the rate or duration of ventricular tachycardia that occurred or whether the ventricular tachycardia was monomorphic or polymorphic. Because all patients with ventricular tachycardia requiring cardioversion or defibrillation and all patients with ventricular fibrillation were analyzed together, it is possible that differences existed between patients with different types of ventricular tachycardia or between patients with ventricular tachycardia and ventricular fibrillation.

Conclusions. Ventricular tachycardia and fibrillation in the absence of heart failure and hypotension are infrequent among patients treated with rt-PA, occurring in 1.9% of patients who were without congestive heart failure or hypotension during the 24 h after admission to the TIMI II trial. The low overall frequency of these arrhythmias in the study group suggests that reperfusion does not increase the incidence of these arrhythmias in the clinical setting. Angiographic findings in patients randomly assigned to the invasive strategy reveal that reperfusion does not increase, and may in fact decrease, the occurrence of ventricular tachycardia and fibrillation. The 21-day mortality rate in patients with ventricular tachycardia and fibrillation was elevated (20.4%) compared with the mortality rate in patients without these arrhythmias (1.6%). Many (4 of 10) of the deaths occurred as a result of inability to resuscitate the patient from the index arrhythmia. No difference was observed in the proportion of patients with a left ventricular ejection

fraction >55% at hospital discharge in the groups with and without ventricular tachycardia or fibrillation. However, more patients with these arrhythmias died before undergoing radionuclide ventriculography. Therefore, whether a relation exists between ejection fraction and the occurrence of ventricular tachycardia and fibrillation cannot be determined from this study. In patients who survived 21 days after myocardial infarction, no difference in mortality was observed during the following year.

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